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09/590,284	06/09/2000	David M. Goldenberg	018733-0967	3453

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EXAMINER
ROARK, JESSICA H

ART UNIT	PAPER NUMBER
1644	19

DATE MAILED: 04/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/590,284	Applicant(s) GOLDENBERG ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *6,8-11 and 16-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,12-15,37 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 2/5/03 (Paper No. 18), is acknowledged.
Claims 1 and 12 have been amended.
Claims 1-38 are pending.

Claims 6, 8-11 and 16-36 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected species.

Claims 1-5, 7, 12-15 and 37-38 *are under consideration in the instant application.*

2. This Office Action will be in response to applicant's arguments, filed 2/5/03 (Paper No. 18). The rejections of record can be found in the previous Office Action (Paper No. 16).

It is noted that New Grounds of Rejection are set forth herein.

Claim Rejections - 35 USC § 112 first paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's comments, filed 2/5/03, that supporting documentation establishing deposit of the LL2 antibody was forwarded with the reply filed 2/5/003 is acknowledged.

However, no associated documentation was found as part of the instant file. In the absence of the necessary deposit information and associated assurances, the rejection of record is maintained, as reiterated below:

> It is apparent that the LL2 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines which produce these antibodies. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, Applicant is required to assure that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications (see 37 CFR 1.808 (a)(2) and MPEP 2410-2410.01).

Amendment of the specification to disclose the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, Applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

NOTE THE CURRENT ATCC DEPOSITORY ADDRESS:
American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209

If the original deposit is made after the effective filing date of an application for patent, Applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state that the biological material which is deposited is the biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See 37 CFR 1.804(b) and MPEP 2406.

While it is acknowledged that the LL2 antibody is well known in the art, it is unclear if the antibody is readily available. Applicant is requested to make of record evidence indicating that the LL2 antibody is in fact readily available to the public.

35 U.S.C. §§ 102

5. Applicant's amendment, filed 2/5/03, has obviated the rejection of claims 1-2, 4, 7 and 14 under 35 U.S.C. 102(e) as being anticipated by Aruffo et al (US Pat. No. 6,051,228, of record) by limiting the claims to the B cell antigens CD19, CD20 or CD22.

Applicant's comments in the Response filed 2/5/03 that CD40 is not a B cell antigen because CD40 is expressed on cells other than B cells is noted.

The Examiner acknowledges that CD40 is expressed on cells other than B cells, as taught by Aruffo et al. However, the claims were drawn to methods employing "at least one antibody to a B cell antigen", not at least one antibody to an antigen expressed only on B cells. CD40 is a B cell antigen. The fact that CD40 is expressed on other cell types does not alter the fact that CD40 is expressed on B cells. Thus the Examiner maintains that a teaching of an anti-CD40 antibody for treatment of multiple sclerosis did meet the limitations of the claims prior to their amendment on 2/5/03 to limit the claims to the B cell antigens CD19, CD20 or CD22.

Claim Rejections – 35 U.S.C. § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-4, 7, 12-15 and 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Aruffo et al (US Pat. No. 6,051,228, of record), Meyer et al. (EP 0332865 A2, of record), Anderson et al. (US Pat. No. 5,776,456, of record), Tedder et al. (US Pat No. 5,484,892, of record) and The Merck Manual of Diagnosis and Therapy (Seventeenth Edition, Beers et al. eds., Merck Research Laboratories, Whitehouse Station, NJ, 1999; Chapter 180 "Demyelinating Diseases", pages 1474-1476, of record).

Applicant's arguments, filed 2/5/03, have been fully considered, but have not been found convincing for the reasons of record set forth in Paper No. 16.

Applicant argues that Aruffo et al. do not teach a method of treating multiple sclerosis by administering at least one antibody to a B cell antigen because CD40 is expressed on cells other than B cells.

Applicant further argues in view of web page discussion that CD40 is a costimulatory molecule and is therefore not a B cell antigen like CD22, CD20 or CD19. Applicant asserts that CD22, CD20 and CD19 are specific to one B cell type, unlike CD40; and concludes that Aruffo et al. therefore does not provide a teaching in view of which it would have been obvious to substitute the teachings of the other references.

Applicant further argues that the mechanism of action by which the two references which address treatment of an autoimmune disease - Aruffo et al. and Tedder, differ, and that Aruffo et al. only teach a mechanism that involves the inhibition of humoral responses to T cell dependent antigens.

Applicant's arguments will be addressed in the context of a reiteration of the rejection of record in Paper No. 16. It is noted that the instant amendments to claims 1 and 12 do not affect the rejection of record in view of the elected species.

As previously noted, the claims as limited to the elected species are drawn to a method of treating multiple sclerosis (MS) comprising administering a therapeutic composition comprising a naked anti-CD20 antibody, a naked anti-CD22 epitope B antibody and the cytokine IFN-β.

Aruffo et al. teach a method of treating multiple sclerosis (MS) by administering a chimeric or humanized antibody to the CD40 antigen (see entire document, e.g., columns 21-22 and in particular column 21 at lines 25-31). Aruffo et al. teach that CD40 is a B cell determinant expressed on B cells (e.g., column 1 at lines 14-22, and that antibody to CD40 depletes B cells when administered *in vivo* (e.g., column 9 at lines 46 and column 12 at lines 37-55). Aruffo et al. teach that the anti-CD40 antibody is administered as a composition comprising a pharmaceutically acceptable carrier (e.g., columns 21 to 22) and that anti-CD40 is administered in vivo at a 10 to 100 mg/dose (e.g. column 12 at lines 35-45). Aruffo et al. teach that the compositions comprising the anti-CD40 antibody may be administered intravenously, or by other parenteral routes (e.g., column 21 at lines 32-36).

As noted supra, CD40 is a B cell antigen because although it is not expressed solely on B cells (i.e., the Examiner acknowledges that CD40 is expressed on other cells, as taught by Aruffo et al. at column 1, lines 14-40), CD40 is expressed on B cells and therefore meets the limitation "a B cell antigen" as previously recited.

For clarification, it is also noted that the "one antigen specificity per cell" quoted by Applicant is in reference to the specificity of the B cell antigen receptor, which is the membrane bound form of an antibody and differs from B cell to B cell. CD22, CD20 and CD19, like CD40, are all expressed by B cells irrespective of the specificity of the B cell antigen receptor, and are not, contrary to Applicant's assertions, specific to one B cell "type".

Applicant's comments regarding the mechanism of action of antibody targeting of CD40 for inhibition of humoral immune responses to T cell dependent antigens are also acknowledged. The Examiner acknowledges that antibody to CD40 does result in the inhibition of the humoral immune response to T cell dependent antigens. The Examiner notes that anti-CD40 antibody inhibits the humoral immune response both by depleting the B cells (i.e., the cells that produce the "humoral immune response") and by interfering with the CD40/CD40L interaction between B cells and T cells (costimulation).

Aruffo et al. clearly appreciate the effect of anti-CD40 antibody on both direct reduction of B cell numbers and on inhibition of the B cell:T cell interaction that leads to amplification of the humoral immune response (see e.g., column 9 at line 46 and column 12 at lines 37-55 regarding anti-CD40 antibody mediated depletion of B cells; and note that the discussion at columns 21-22 note that anti-CD40 antibodies find use in treating antibody mediated and/or T cell mediated disorders).

As also acknowledged previously, Aruffo et al. do not teach combining the anti-CD40 antibody in a therapeutic composition comprising a naked anti-CD20 antibody, a naked anti-CD22 epitope B antibody and the cytokine IFN-β.

However, the importance of combination therapy in the regulation of B cell responses to treat MS would have been obvious to the ordinary artisan at the time the invention was made.

Meyer et al. teach that the B cell response in mammals can be suppressed by administering antibodies, either unconjugated (i.e., "naked", see page 3 at line 31) or conjugated, to surface antigens of the B cell (see entire document, e.g., Abstract and claims). Meyer et al. also teach utilizing antibodies to more than one B cell surface marker because not all B cell populations share the same antigen markers (see especially page 3 lines 26-30).

Anderson et al. teach the production of a chimeric anti-CD20 antibody and the use of this antibody to deplete nonmalignant B cells *in vivo* (see entire document, especially Examples II and III on pages 27-page 37). Anderson et al. also teach that CD20 is expressed early in B cell development and remains until plasma cell differentiation (e.g., page 8, 2nd full paragraph). Anderson et al. teach that the chimeric anti-CD20 antibody is well tolerated when administered parenterally in a dosage of 10-500 mg/m^2 (e.g., columns 28-29). Anderson et al. also teach that for therapy repeated parenteral (i.e., intravenous) dosages should be administered (e.g., column 29, especially lines 31-49). Anderson et al. also contemplate the administration of the chimeric anti-CD20 antibody in combination therapy (see e.g., columns 29-32, especially column 32 at lines 7-23).

Tedder et al. teach antibodies to the B cell surface protein CD22 and their use in blocking B cell function (see entire document, e.g., "Summary of the Invention" at columns 2-3). Tedder et al. review that CD22 is expressed on the surface of the population of B cells that are the mature cells, and that expression of CD22 is increased on the surface of B cells that are activated (see "Background of the Invention" at columns 1-2). Tedder et al. teach that anti-CD22 antibodies can be used to for therapy of autoimmune diseases (see e.g., column 2 at lines 59-64 and columns 6-7), and that anti-CD22 antibodies can be administered in combination with other antibodies (see especially column 6 at lines 55-65).

In addition, Tedder et al. also teach antibodies to epitope "B" of CD22 (e.g., the antibody HD6 at column 2 lines 26-42 and the HB22-33 antibody at column 11, Table III), and that the anti-CD22 antibodies could be chimeric and humanized antibodies (e.g., column 5 at lines 45-60). Tedder et al. also teach parenteral (e.g., intravenous) administration of the anti-CD22 antibodies and that the dosage should be about 1 mg/kg body weight (see bridging paragraph of columns 6-7).

Applicant argues that the anti-CD22 antibodies of Tedder et al. act by blocking the adhesive function of CD22, and further argues that since this function is distinct from that of CD40; the ordinary artisan would not have been motivated to substitute of combine the antibodies of Tedder et al. and Aruffo et al.

The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

That different antibodies block different aspects of B cell function is not a contraindication to their co-administration. The ordinary artisan at the time the invention was made was aware that inhibiting multiple steps along a pathway to an endpoint (e.g., suppression of humoral immunity) provided more efficacious inhibition of the endpoint.

Meyer et al. teach that in order to effectively regulate B cell responses in vivo, antibodies to multiple B cell surface antigens should be combined. Anderson et al. and Tedder et al. teach naked (i.e., unconjugated) antibodies to CD20 and CD22 that can each be used to regulate B cell responses *in vivo*. Thus the ordinary artisan at the time the invention was made would have been motivated to utilize a therapeutic composition comprising not only the anti-CD40 antibody of Aruffo et al., but also the art-recognized effective anti-CD20 and anti-CD22 antibodies in order to increase the number of B cell populations targeted by the therapeutic composition and provide a more effective therapeutic composition for use in a method of treating MS.

The combination of Aruffo et al., Meyer et al., Anderson et al. and Tedder et al. differ from the instant invention by not teaching administration of the cytokine IFN-β.

However, the Merck Manual of Diagnosis and Therapy recognized the cytokine IFN-β as a standard therapy for MS (see pages 1474-1476, especially page 1476). The Merck Manual teaches that administration of the cytokine IFN-β reduces the frequency of relapses in patients with MS. Therefore, the ordinary artisan at the time the invention was made would have found it obvious to administer the cytokine IFN-β concurrently or separately with any other therapeutic composition for treating MS. The ordinary artisan would have been motivated to also provide the cytokine IFN-β. since it is an art-recognized therapy that helps reduce the frequency of relapse.

Thus the ordinary artisan at the time the invention was made, armed with the combined teachings of the references would have been motivated to combine the antibodies of Anderson et al. and Tedder et al. with the anti-CD40 antibody of Aruffo et al. to target multiple components of the MS immune response with an expectation that the combined therapy would be more efficacious than the single therapy approach. In addition, recognizing that administration of the cytokine IFN-β was an art established therapy for treatment of MS, the ordinary artisan would have been motivated to retain it along with any other therapeutic administered. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection of record is therefore maintained.

8. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Aruffo et al (US Pat. No. 6,051,228, of record), Meyer et al. (EP 0332865 A2, of record), Anderson et al. (US Pat. No. 5,776,456, of record), Tedder et al. (US Pat No. 5,484,892, of record) and The Merck Manual of Diagnosis and Therapy (Seventeenth Edition, Beers et al. eds., Merck Research Laboratories, Whitehouse Station, NJ, 1999; Chapter 180 "Demyelinating Diseases", pages 1474-1476, of record) as applied to claims 1-4, 7, 12-15 and 37-38 above, and further in view of Leung et al. (Mol. Immunol. 1995; 32(17/18):1413-1427, of record).

Applicant's arguments, filed 2/5/03, with respect to the primary references have been full considered but have not been found convincing for the reasons set forth supra.

Applicant does not appear to further argue the rejection of claim 5 with respect to Leung et al.

The amendment to claims 1 and 12, filed 2/5/03, does not alter the rejection of record.

The claims are still drawn to a method of treating multiple sclerosis (MS) comprising administering a therapeutic composition comprising a naked anti-CD20 antibody, a naked anti-CD22 epitope B antibody and the cytokine IFN-β, wherein the anti-CD22 epitope B antibody is the murine, chimeric, humanized or human LL2 antibody.

As previously noted, Leung et al. teach the production of a humanized form of the LL2 antibody and compare it to the parental murine LL2 antibody and a chimeric form of the LL2 antibody (see entire document, e.g., Figure 5). Leung et al. teach that several anti-CD22 antibodies were available for *in vivo* diagnostic and therapeutic use, but that the humanization of LL2 made it a preferred antibody for clinical applications (see "Discussion" on pages 1420-1425, especially the paragraph bridging pages 1424 and 1425).

Therefore, the ordinary artisan at the time the invention was made would have found it obvious to substitute the chimeric or humanized LL2 antibody for the anti-CD22 antibodies of Tedder et al. The ordinary artisan would have been motivated to make this substitution because of the reduced side effects (HAMA antibodies) associated with administering a humanized versus a rodent antibody. Since the humanized LL2 antibody recognized the same specificity (epitope B of CD22), the ordinary artisan would have had a reasonable expectation that the humanized LL2 antibody would function at least as well as the anti-CD22 antibody of Tedder et al. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection of record is therefore maintained.

Conclusion

9. No claim is allowed.

10. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
April 1, 2003

PHILLIP GAMBEL

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